

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN,
LOSARTAN, AND IRBESARTAN
PRODUCTS LIABILITY
LITIGATION

MDL No. 2875

THIS DOCUMENT RELATES TO ALL
CASES

HON. ROBERT B. KUGLER
CIVIL NO. 19-2875 (RBK)

**PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT*
MOTION TO PRECLUDE OPINIONS OF
DEFENSE EXPERT MICHAEL B. BOTTORFF, PHARM.D.**

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I. INTRODUCTION

Defendants retained and disclosed Michael B. Bottorff, Pharm.D., as an expert in pharmacokinetics and pharmacology. (Def. Br. at 1, [ECF 1789](#)). Plaintiffs do not dispute that Dr. Bottorff is experienced in the field of pharmacology and the treatment of cardiovascular issues with pharmaceutical drugs, including valsartan. (Def. Br. at 6). However, this litigation is about NDMA/NDEA, valsartan just so happens to be the vehicle delivering the NDMA/NDEA. Dr. Bottorff offers opinions on the metabolism and dose response of mutagenic carcinogens (NDMA/NDEA), but applied the same methodology to these mutagenic carcinogens as he applies to non-mutagenic pharmaceutical drugs, which is methodologically unsound.

II. ARGUMENT

A. Lack of Experience with Genotoxic Carcinogens

Defendants claim that “Plaintiffs’ statement that ‘the only experience that Dr. Bottorff had with a genotoxin carcinogen was prescribing Actos’ is untrue” and that Dr. Bottorff reviewed other potentially immunosuppressive drugs prior to this litigation. (Def. Br. at 19). In reality, Dr. Bottorff wrongly assumed that because immunosuppressives can cause cancer that they might be genotoxic.

Q. You noted lidocaine earlier. Is lidocaine a genotoxic carcinogen?

A. I don’t think so. It’s just an example of a drug that has a very high first-pass metabolism, and so giving it orally will never produce any post-liver effect. So it’s a good example in that regard.

Q. But the only genotoxic carcinogen that you have experience with is Actos, correct?

A. No. I also mentioned the immunosuppressive drugs for heart transplant patients. But that’s pretty much the extent.

Q. Those are genotoxins?

A. I'm not sure their mechanism of cancer production is genotoxic. But they are carcinogenic.

Q. Okay. So the only genotoxic carcinogen that you have experience with is Actos?

A. In – in that specific genotoxic sense, yes.

(Bottorff Dep. at 377:20-379:10, [ECF 1712-3](#), Ex. A (emphasis added)). Prescription of Actos is the only experience that Dr. Bottorff has with a genotoxic carcinogen. Defendants' only citations to support their proposition that Dr. Bottorff has experience with other genotoxins are to another part of Dr. Bottorff's deposition where he again incorrectly equated immunosuppression to genotoxicity (Bottorff Dep. at 315:8-18) and to part of his deposition where he testified that he probably hasn't filled a prescription since 1982. (Bottorff Dep. at 49:2-16).¹ Regardless of whether Dr. Bottorff actually filled a prescription of Actos, his only experience with a genotoxin prior to this litigation was reviewing the study that found an association between Actos and bladder cancer. (Bottorff Dep. at 379:23-380:6). This lack of experience and knowledge informs the Daubert inquiry.

B. Dr. Bottorff Applied a Dose Conversion Formula Intended for Non-Carcinogens

Defendants claim that "Dr. Bottorff's dose conversion to a 70 kg (154 lbs) human is generally accepted as valid in the scientific community and has repeatedly been put to non-judicial uses." (Def. Br. at 29 (emphasis added)). To support their position, Defendants cite *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 593-94 (1993) and *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d. Cir. 1994), neither of which discuss 70 kg being the appropriate weight when converting the dose of a carcinogenic substance. Instead, the cited case law supports the proposition that a District Court should take into account "whether the methodology has been

¹ Dr. Bottorff also testified that to the best of his knowledge he kept all of his patients on Actos. (Bottorff Dep. at 381:6-11).

generally accepted in the scientific community.” *See Paoli*, 35 F.3d at 742. Defendants then cite two pieces of literature noting 70 kg is the average adult weight.² Plaintiffs do not dispute that utilizing 70 kg in a dose conversion formula for non-carcinogenic substance is a well-accepted methodology. However, utilizing 70 kg in a dose formula for a carcinogenic substance is not an accepted methodology. In the FDA’s 2018 *Guidance for Industry: M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* 50 kg is utilized in a dose formula for a mutagenetic³ carcinogen. ([ECF 1711-6](#) at 22, 37, 39, 46, 47, 53, 62, 67, 71, 72, 78, 84, 89, 97, 101, 105, 106, 117). Utilizing 50 kg in a dose formula for a carcinogenic substance is a well-accepted methodology outside of the United States as well. (2015 European Medicals Agency, Ex. H).

Defendants’ argument that dose conversions to a 70 kg human is *generally* accepted as a valid methodology in the scientific community is misleading. The methodology (70 kg) is accepted when applied to one issue (converting a non-carcinogenic substance) and not accepted when applied to another issue (converting carcinogenic substances). The methodology must be scientifically valid or generally accepted as it is applied to the facts in issue. *See Daubert*, 509 U.S. at 592-93. Dr. Bottorff’s methodology is not generally accepted when dealing with carcinogenic substances.

Dr. Bottorff admitted that his methodology would always overestimate the amount of a carcinogen a human would need to be exposed to when converting from an animal. (Bottorff Dep. at 208:10-15). That is a striking admission that colors the entire methodology. Defendants argue that Dr. Bottorff would have come to the same conclusions had he followed the accepted

² Defendants cited literature is silent on how to appropriately convert doses.

³ Of note, all mutagens are genotoxins, but not all genotoxins are mutagens. NDMA/NDEA are mutagens, though they are also frequently referred to as genotoxins.

methodology of utilizing 50 kg when converting the dose of a carcinogenic substance.⁴ (Def. Br. at 29). Defendants' argument misses the mark, as the overarching subject of Rule 702 "is the scientific validity and thus the evidentiary relevance and **reliability**—of the principles that underlie a proposed submission. The focus, of course, must be solely on principles and methodology, **not the conclusions that they generate.**" *Daubert*, 509 U.S. at 594-95 (emphasis added). Dr. Bottorff's application of an inappropriate methodology is evidence of him opining outside the field of his expertise, and supports Plaintiffs' position that his opinions are not reliable. While "general acceptance" is no longer the standard for admitting expert testimony, it can have a bearing on the inquiry. *Id.* at 594. A "reliability assessment does not require, although it does permit, explicit identification of a **relevant** scientific community and an express determination of a particular degree of acceptance within that community." *Id.* (emphasis added). The relevant scientific community at issue is one that deals with mutagenic carcinogens. Dr. Bottorff can not reliably opine as to mutagenic carcinogens and should therefore be excluded from testifying in this litigation.

C. Dr. Bottorff Improperly Extrapolated from Rats to Humans at a One-to-One Ratio

Dr. Bottorff provided further evidence that he can not reliably opine on mutagenic carcinogens when he improperly extrapolated the dose of a mutagenic carcinogen (NDMA/NDEA) from rats to humans at a one-to-one ratio (dose is determined as to a 1 kg rat and then that base dose is added for every 1 kg increase in weight). (Bottorff Dep. at 272:3-7). Dr. Bottorff's deposition testimony highlights the unreliability of the opinions he seeks to offer:

Q. And what was your basis that one-to-one ratio was appropriate to use for NDMA?

⁴ This calculation error is also compounded by other calculation errors that Dr. Bottorff made and the fact that he only applied his formula to doses that did not demonstrate an association with cancer in a rat.

A. It's just the best that we have. **We don't have any other method of conversion** based on some other physiologic factor. It's how the animals were dosed. They were dosed in milligrams per kilogram.

Q. But you have no basis for why that's appropriate to extrapolate them to humans based on weight?

A. Well, as I've already said, **we are not sure that extrapolating these animal data to humans is accurate and the right thing to do to begin with.** We have some missing parts. We've got the milligram per kilogram dose in the animals, what dose didn't cause cancer, we have the weight, the average weight of a human adult, and then we have how much microgram quantities were in the valsartan product. So there's that missing link connection that is an assumption that is being made.

(Bottorff Dep. at 272:8-273:9 (emphasis added)).

While Dr. Bottorff might not know if extrapolating from animals to humans is the right thing to do or what method should be used, the relevant scientific community does. In 2002, the World Health Organization (WHO) stated:

Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure response developed on the basis of experimental data in animals, since it's highly probable that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite.

(2002 WHO N-Nitrosodimethylamine, [ECF 1712-4](#), Ex. B). Even though Dr. Bottorff listed the 2002 WHO document on his materials considered, he was unaware of the above quote, and admitted that had he been aware of it that he would have potentially altered his methodology. (Bottorff Dep. at 310:23-314:15).⁵ This is yet another significant methodological concession.

Defendants then argue that because Dr. Bottorff didn't reference "scaling for body-surface area, Dr. Bottorff's extrapolation from mg/kg on a one-to-one basis from rats to humans was proper

⁵ Defendants falsely claim that Dr. Bottorff critically analyzed all relevant mechanistic literature on NDMA and NDEA. (Def. Br. at 9).

and is a standard approach for comparing doses given to animals.” (Def. Br. at 33). Again, this is only a standard approach when extrapolating doses of a non-carcinogenic substance. Defendants provide no actual explanation or support as to why Dr. Bottorff’s one-to-one extrapolation is appropriate. Instead, Defendants criticize Plaintiffs for not explaining appropriate extrapolation formulas for mutagenic carcinogens. (Def. Br. at 33).

Assuming that it is appropriate to extrapolate NDMA/NDEA doses from rats to humans, it should be done at a less than one-to-one ratio. The Environmental Protection Agency (EPA) notes to use “BW^{1/1} (body weight at a one-to-one ratio) for non-cancer endpoints and, at various times BW^{2/3} or BW^{3/4} for cancer endpoints to normalize dose across species.” (2011 EPA, Ex. I at ix (explanatory parenthetical added)). Again, Dr. Bottorff’s methodology is only appropriate when applied to a non-carcinogenic substance.

However, scaling from rats to humans even at these reduced ratios is inappropriate due to NDMA/NDEA’s mechanism of action, as explained by the WHO above and the EPA below:

BW^{3/4} scaling would apply most appropriately to those exogenous substances for which the unmetabolized parent or a stable metabolite is the relevant toxic species and clearance is according to first-order process. Conversely, the applicability of BW^{3/4} scaling is less well supported when toxicity is a consequence of exposure to a very reactive parent compound or metabolite that is not removed from the site of formation by biological processes (e.g., subsequent metabolism) but chemically reacts with cellular constituents.

(Ex. I at 11). NDMA is a very reactive parent compound and its carcinogenicity is primarily mediated through the generation of an active metabolite that chemically reacts with cellular constituents to permanently alter DNA.

Extrapolating dose of NDMA/NDEA from rats to humans based on body weight is inappropriate, especially at the one-to-one ratio applied by Dr. Bottorff. In deposition, Dr. Bottorff admitted that he didn’t investigate whether mutagenicity could impact interspecies scaling.

(Bottorff Dep. 164:9-13). As such, Dr. Bottorff improperly applied the methodology he is accustomed to applying in his field of expertise (non-carcinogenic substances) to a field outside of his expertise (mutagenic carcinogens). Dr. Bottorff can not reliably opine on mutagenic carcinogens.

D. Dr. Bottorff Applied his Improper Conversion and Extrapolation Methods Only to Doses That Were Not Associated With an Increased Risk of Cancer in Rats

Defendants claim that “Plaintiffs erroneously assert Dr. Bottorff ‘only looked for studies that would support his opinion that the levels of NDMA in contaminated valsartan don’t cause cancer...’” (Def. Br. at 23). Dr. Bottorff clearly testified “But again, **I was looking for doses that didn’t cause cancer, not doses that did.**” (Bottorff Dep. at 297:18-20). Defendants even admit in their brief that Dr. Bottorff “pinpointed dose levels that did not cause cancer in certain treatment groups.” (Def. Br. at 13). This is an inherently biased starting position, as it allows him to cherry-pick studies in which higher doses (mg/kg) of NDMA were not found to cause cancer, while ignoring studies in which lower doses of NDMA were found to cause cancer. Dr. Bottorff then applied his improper conversion and extrapolation methods only to doses that were low enough to be unable to detect an increased risk of cancer in some rat studies. (Def. Br. at 13). Dr. Bottorff’s methodology is biased and unreliable.

E. Dr. Bottorff’s Opinion that NDMA Has a Dose Threshold is Not Generally Accepted by the Relevant Scientific Community

Defendants argue that “Dr. Bottorff is sufficiently qualified to interpret animal studies for dose-response relationships and opine whether there is a dose threshold below which there is no evidence of carcinogenicity—a practice and methodology he has employed for ‘hundreds and hundreds of drugs and compounds throughout his career.’” (Def. Br. at 20). As addressed above, Dr. Bottorff does not have experience with mutagenic carcinogens, and the relevant scientific community does not agree with the application of his methodologies to mutagenic carcinogens.

Dr. Bottorff relied on the *Peto* study to opine that NDMA has a dose threshold, while he casually admitted that *Peto* showed that there was **not** a dose threshold for NDMA. Dr. Bottorff testified:

And I would just like to add that this is an era at the time where ***everyone pretty much already believed that it was linear***. And so to me, [Peto] was trying to not accept that it might not be. And ***I think there are other experts in this field who might*** argue that we have more modern data that dispute a low range linearity relationship.

(Bottorff Dep. at 202:15-203:1 (emphasis added)). Dr. Bottorff's opinions are at odds with the experts in this field, and his inexplicable reliance on *Peto* for a proposition that *Peto* refuted is unsound. Furthermore, Dr. Bottorff's belief that there might be an expert in the relevant field that agrees with him is not a proper basis for a reliable opinion.

F. Dr. Bottorff Ignored Contrary Evidence Regarding NDMA Metabolism

Dr. Bottorff improperly extrapolated rat studies to support his opinion that the levels of NDMA in VCDs cannot clear the liver and reach systemic circulation in humans, while ignoring human studies such as *Fine* that demonstrate NDMA at levels much lower than in most VCDs being able to clear the liver and reach systemic circulation. (*Fine* 1997, [ECF 1789-23](#)). Defendants' contention that the human dietary studies are irrelevant because the NDMA is formed endogenously after the foods are ingested is without merit. (Def. Br. at 32). As explained in the article by *Fine*, endogenous formation of NDMA after ingesting food would occur in the stomach; therefore, the NDMA would still be subject to first-pass metabolism by the liver. (*Fine* at 754; *See* Def. Br. at 8). Human studies not considered by Dr. Bottorff clearly demonstrate the ability of NDMA at levels in VCDs to clear the liver and reach systemic circulation.

Dr. Bottorff's testimony elicited by the defense on this subject further demonstrated that Dr. Bottorff's area of expertise is with non-carcinogenic drugs such as valsartan, not mutagenic carcinogens such as NDMA/NDEA.

Q. I was asking about, did you have to determine the first-pass metabolism of both valsartan and then NDMA –

A. Yeah, it's easier for valsartan because it's supposed to get through the liver and do its pharmacologic effect so you can measure the bloodstream to assess bioavailability. **For NDMA, that assessment is not as exact a science**, except for a couple small rat studies that look at it, because you don't want it to get into the systemic circulation. So – and the dose is low enough that you get first complete first-pass metabolism, you couldn't measure it in the bloodstream.

(Bottorff Dep. at 359:17-360:11).

III. CONCLUSION

For the foregoing reasons, Dr. Bottorff can not reliably opine on mutagenic carcinogens, and should be precluded from offering any such opinions. Dr. Bottorff is qualified to discuss the metabolism and dosing of non-carcinogenic substances, such as valsartan. However, allowing such standalone testimony would only confuse and mislead the jury, as the general causation questions in this litigation relate to NDMA/NDEA, not valsartan. The issues that must be explained to a jury are already incredibly complex; therefore, irrelevant testimony about valsartan poses an even greater risk of confusing the jury. Without the ability to reliably opine on mutagenic carcinogens, Dr. Bottorff should be excluded entirely from testifying in this litigation.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on January 6, 2022, a true and correct copy of the foregoing was filed and served upon all counsel via operation of the CM/ECF system for the United States District Court for the District of New Jersey.

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